CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-224

CORRESPONDENCE

NEW CORRESP
NC to
FAX

September 18, 1998

TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

RE: **ANDA 75-224**
Clobetasol Propionate Topical Solution USP, 0.05%
Facsimile Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on October 8, 1997, pursuant to 21 CFR 314.70, and our Amendment of March 23, 1998. Reference is also made to the Agency's letter of September 4, 1998, in which it is stated that the application is deficient and, therefore, not approvable under Section 505 for the following reasons:

A. Deficiencies:

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Specifically Chemistry discussion

COMMENT #7

[redacted] is a [redacted] in the drug product and should be analyzed at each test point station for the stability samples. **Please revise your drug product release and stability specifications to include testing, limits and specification to determine the [redacted] content.**

Response

Release and stability specifications have been revised to include the test and limits for [redacted] content. Please refer to **supplementary pages 20 - 22.**

This completes our response to the Agency's deficiency letter dated September 4, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

This Facsimile Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

TARO PHARMACEUTICALS INC
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

SEP 4 1998

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-224 APPLICANT: Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Clobetasol Propionate Topical Solution, USP, 0.05%

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. a) Please perform the test and provide the limits/specification for the related compound A (known impurity) on your COA, using your standard and, in addition, commit to provide the complete monograph test results of clobetasol propionate drug substance using USP reference standard when available.

   b) You have submitted only results from the overload injection (page 4). Please provide the completed COA for the house standard, (L) 2220-R, which was used in the subject application.

2. Your revised specifications for the drug substance clobetasol propionate show that you have removed the test and specification for OVI from your COA. OVI testing is required by USP for this drug substance. Please provide test, limits/specification or a statement from the manufacturer to ensure that no volatiles are used in the manufacture of the drug substance.

3. Please provide the test method used for the analysis of residual solvents.

4. Your proposed specifications for residual solvents include limits for dichloromethane which is an OVI. Please separate the OVI's from the residual solvents and provide their test, limits and specifications on your COA.

5. Please update your specifications of purified water according to USP 23, supplement 8 and provide them on your COA.

6. You have provided the tentative limits for the individual and total degradation products for your stability samples. Please tighten the limits for degradation products based on your stability data.

7. is a preservative in the drug product and should be analyzed at each test point station for the stability samples. Please revise your drug product release and stability specifications to include testing, limits and specification to determine the ntent.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

July 13, 1998

ORIG AMENDMENT
N/AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857

Re: **ANDA 75-224**
Clobetasol Propionate Topical Solution USP, 0.05%
Telephone Correspondence

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on October 8, 1997, pursuant to 21 CFR 314.70. Reference is also made to the phone call on July 10, 1998 from Ms. Lillie Golsen of the Labeling Division (301) 827-5846 in which she requested clean copies of the package insert, as well as the bottle and carton for the 50 mL size.

As per this request, please find enclosed 12 final printed package inserts, 12 final printed bottle labels, and 12 final printed carton labels. Please note that all of these are actual size labels.

If you should have any further questions, please do not hesitate to contact me. This concludes our response to the Agency's phone call of July 10, 1998.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

enc./S.Antoniuk

RECEIVED
JUL 14 1998
GENERIC DRUGS

98SLA009.DOC
07/13/98 4:32 PM

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-224 APPLICANT: Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Clobetasol Propionate Topical Solution, USP, 0.05%

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

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   b) You have submitted only results from the overload injection (page 4). Please provide the completed COA for the house standard, (L) 2220-R, which was used in the subject application.

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3. Please provide the test method used for the analysis of residual solvents.

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5. Please update your specifications of purified water according to USP 23, supplement 8 and provide them on your COA.

6. You have provided the tentative limits for the individual and total degradation products for your stability samples. Please tighten the limits for degradation products based on your stability data.

7. l is a in the drug product and should be analyzed at each test point station for the stability samples. Please revise your drug product release and stability specifications to include testing, limits and specification to determine the ntent.

Sincerely yours,

/S/ 9/11/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

March 23, 1998

TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

ORIG AMENDMENT
N | AC

Telephoned Korman Sachs and requested letter quality FPL
K Sachs 3/25

RE: **ANDA 75-224**
Clobetasol Propionate Topical Solution USP, 0.05%
Major Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on October 8, 1997, pursuant to 21 CFR 314.70. Reference is also made to the Agency's letter of February 2, 1998, in which it is stated that the application is deficient and, therefore, not approvable under Section 505 for the following reasons:

A. Deficiencies:

Raw material controls - active and inactive ingredients

Page(s) 12

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Mfg and processing / specifications

Labeling Deficiencies

1. CONTAINER (25 mL and 50 mL)

a. Revise to include on the principal panel in prominent lettering, "FOR USE ON THE SCALP".

b. Revise the "Contains" statement to read, ...0.05% (0.5 mg/g) in a...

c. Revise the "See package insert" statement to read, "USUAL DOSAGE: See package insert ..."

d. Revise "Do not use near an open flame" to appear in equal prominence as the rest of your storage recommendation .

2. CARTON (25 mL and 50 mL)

See CONTAINER comments.

3. INSERT

a. DESCRIPTION

i. Revise the chemical name to the second name listed in the official monograph for clobetasol propionate in USP 23, supplement # 2 .

ii. Revise the first sentence of the third paragraph to read, ... molecular formula...molecular weight of 466.98.

b. CLINICAL PHARMACOLOGY

Revise the first sentence of the second paragraph to read, Clobetasol propionate, a corticosteroid, has been... (Note: add comma)

c. INDICATIONS AND USAGE

Revise so that the ultimate sentence of the first paragraph, "This product is not. . ." is a new paragraph.

d. PRECAUTIONS (General)

Revise the first sentence of the eighth paragraph to read, "As with other potent topical corticosteroids, clobetasol.. (Note: add comma)

e. ADVERSE REACTIONS

Revise the second paragraph to read, "...sensation, which occurred in approximately 10% of the patients; scalp pustules, which occurred in approximately 1% of the patients; and tingling and folliculitis, each of which occurred in 0.7% of the patients. Less...and eye irritation.

Please revise your labels and labeling, as instructed above, and submit in final print.

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Response

The labels and labeling have been revised as instructed above. The following has been provided:

Twelve (12) final printed labels:

- 25 mL bottle labels (**supplementary pages 137 - 148**)
- 25 mL carton labels (**supplementary pages 149 - 160**)
- 50 mL bottle labels (**supplementary pages 161 - 172**)
- 50 mL carton labels (**supplementary pages 173 - 184**)
- Package insert (plastic pouch with the **supplementary page 185**)

Side-by-side comparison of the proposed labeling with the last submission with all differences annotated and explained is provided in **supplementary pages 186 - 202.**

This completes our response to the Agency's deficiency letter dated February 2, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

TARO PHARMACEUTICALS INC
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

FEB - 2 1998

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-224 **APPLICANT:** Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Clobetasol Propionate Topical Solution, USP, 0.05%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Raw material controls - active and inactive ingredients:

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

specification / Mfg / processing

method validation.

Stability:

22. Stability sample storage conditions provided in the pre and post approval stability protocol are different from those in your stability testing program and CoA. Please clarify.

23. a. Please remove all references to tubes and related SOP for sampling and testing from your stability section.

    b. Please provide the correct sampling and testing plan for this submission.

24. Please include the orientation of samples in your post approval stability protocol.

25. Please establish and revise your stability specifications for degradation products (individual and total) based on available data.

26. Please provide all available room temperature stability data.

27. Please revise your drug product release and stability specifications to include limit and specification for isopropyl alcohol content.

Environmental Impact Considerations/Categorial Exclusion:

28. Please provide a statement explaining that Bramalea site is in compliance with environmental regulations.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You are advised that the use of in-house analytical methods for testing the drug substance and drug product do not relieve you from meeting the compendial standards. In the event of a dispute, the USP method will be used in analyzing the drug substance and drug product.

2. Your bioequivalence waiver request is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with CGMP at the time of approval.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-224 **APPLICANT:** Taro Pharmaceuticals U.S.A., Inc.

DRUG PRODUCT: Clobetasol Propionate Topical Solution, USP, 0.05%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

Page(s) _____

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

specification/Mfg process,
chemistry

Stability:

22. Stability sample storage conditions provided in the pre and post approval stability protocol are different from those in your stability testing program and CoA. Please clarify.

23. a. Please remove all references to tubes and related SOP for sampling and testing from your stability section.

    b. Please provide the correct sampling and testing plan for this submission.

24. Please include the orientation of samples in your post approval stability protocol.

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2. Your bioequivalence waiver request is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with CGMP at the time of approval.

Sincerely yours,

/S/ 1/30/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ARCHIVE

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

NEW CORRESP

November 7, 1997

75-224

Ms. Middleton
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Original Abbreviated New Drug Application (ANDA) for Clobetasol Propionate Topical Solution USP, 0.05 %**

Dear Ms. Middleton:

In response to your communication with Lorraine Sachs of Taro Pharmaceuticals USA Inc., we are providing a revised patent certification to amend the above "ANDA, submitted October 8, 1997. This certification was originally faxed to your attention on November 7, 1997.

If there are any questions regarding this application, or if additional information is required, please contact our US agent:

Taro Pharmaceuticals USA, Inc.,
Attn: Lorraine Sachs
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

RECEIVED
NOV 13 1997
GENERIC DRUGS

Sincerely,
TARO PHARMACEUTICALS INC.

JH/bs for

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/J. Hobbs

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

BIOEQUIVALENCY COMMENTS

ANDA:75-224 APPLICANT:Taro Pharmaceuticals

DRUG PRODUCT: Clobetasol Propionate Topical Solution, 0.05%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-224

Taro Pharmaceuticals USA, Inc.
Attention: Lorraine Sachs
U.S. Agent for: Taro Pharmaceuticals Inc.
5 Skyline Drive
Hawthorne NY 10532

NOV 13 1997

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Clobetasol Propionate Topical Solution USP, 0.05%

DATE OF APPLICATION: October 8, 1997

DATE OF RECEIPT: October 9, 1997

We also acknowledge your correspondence dated November 7, 1997.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

PATENT CERTIFICATION

"NO RELEVANT PATENTS" STATEMENT

Taro Pharmaceuticals Inc. hereby certifies that the patent status of the subject drug, Clobetasol Propionate Topical Solution USP, 0.05%, is as follows:

In the opinion and to the best knowledge of Taro Pharmaceuticals Inc., there are no patents that claim the listed drug referred to in this application, TEMOVATE® (Clobetasol Propionate) Solution, 0.05%, or that claim a use of the listed drug.

This certification is made in accordance with Section 505(j)(2)(A)(vii)(II) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.94(a)(12)(ii).

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

November 7, 1997
Date

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008